EXHIBIT B

Duke | OFFICE of AUDIT, RISK & COMPLIANCE

Duke University
Research Compliance Assurance
Jiang Pro000009555 and Pro000014033
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Clinical Research Unit Management

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School of Medicine Senior Leadership

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ENGAGEMENT TEAM

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INVESTIGATION SUMMARY

OBJECTIVE AND BACKGROUND

At the request of [redacted], M.D. and Wei Jiang, M.D., the Duke Office of Audit, Risk and Compliance (OARC) Research Compliance Assurance (RCA) section assessed compliance with Good Clinical Practice (GCP), applicable U.S. Food and Drug Administration (FDA) regulatory requirements, and institutional policies for protocols Pro000009555, Responses of Myocardial Ischemia to Escitalopram Treatment, and Pro000014033, Research Database/Repository for Blood Samples in Ischemia Understanding Pathophysiological Mechanisms of Mental Stress Induced Myocardial Ischemia. RCA conducted this review after the Psychiatry and Behavioral Sciences assistant research practice manager noted eligibility, data quality and regulatory issues during an internal quality assurance (QA) review of Pro000009555.

RCA visited the Psychiatry research offices in the Duke Clinics building June 4 through June 13, 2018 and July 3 through July 7, 2018. RCA also visited the Investigational Drug Services in the Department of Pharmacy on June 12, 2018. RCA reviewed regulatory documents specific to both studies and drug accountability logs for Pro000009555. Subject study records for 17 of the 310 subjects were selected for initial review. An additional eight subjects were selected after eligibility and data quality issues were identified in the first sample, for a total of 8.1%. Subject records reviewed covered the entire four-year enrollment period and work performed by the majority of research staff listed on the delegation of authority (DOA) log.

RISK AND AREA IMPACT

Pro000009555 is a single center, double-blind randomized study with a placebo arm to assess the efficacy of escitalopram on mental stress-induced myocardial ischemia (MSIMI) in patients with stable ischemic heart disease (IHD). The study also examines the effects of escitalopram on depression symptoms, platelet activity and cardiovascular stress response in relationship to MSIMI. Pro00009555 is a principal investigator (PI)-initiated study funded by National Heart, Lung and Blood Institute (NHLBI) grant RHL085704 and is referred to as the REMIT trial.

Pro000014033 created a repository for specimens collected during the primary trial intended for use in future research studies; it is a PI-initiated and institutionally funded trial, referred to as the REMIT Repository trial.

OARC notes that these are two related but separate Duke University Health System (DUHS) Institutional Review Board (IRB)-approved trials.

The REMIT trial involves a widely used antidepressant in subjects with MSIMI, thereby lowering the overall patient safety risk profile. Since the data are published and both protocols are still active, there may be risk associated with reproducibility of results and integrity of current and/or future publications stemming from data quality issues.

RESULTS

Report results are based on information provided to the RCA team at the time of review, as well as subsequent requests for information needed to conclude on protocol compliance status. RCA recommendations reflect actions needed to achieve compliance with the protocols and GCP, as well as preventative measures to minimize issues going forward. RCA discussed these recommendations with representatives from the Duke Office of Clinical Research (DOCR) and the IRB. Subsequent implementation is left to the discretion of the IRB and Psychiatry leadership.

The full report below is a supplement to the executive summary distributed earlier this week and provides a detailed account of all findings from the fieldwork performed in June and July. This document elaborates on the observations presented in appendix A of the executive summary, and is distributed to team members that may be involved in writing the response, and in implementing both REMIT trial and global recommendations. Please direct any queries to [redacted].

1) OBSERVATION: ELIGIBILITY

Safety Checklist Used to Screen Patients Not Incorporated In the Protocol

An unsigned, undated document called "Safety Checklist" was included in subjects' 302-100, 301-104, 332-109, 330-111, and 342-112, and 369-119 files (24% of reviewed subjects, all accrued toward the end of the study). The safety checklist specifies that patients should not be brought into the ECHO lab if they do not meet the certain criteria listed below:

- Vital signs: BP < 160/100, HR < 90, RR: 24/min temperature: Afebrile. Patient is not an acute distress and not appear frail
- Symptoms: No chest pain or discomfort, no SOB, no new onset or severe headache, no new symptoms since last cardiologist's appointment
- Meds: No anti-depressants/anti-psychotic medications, with a note to notify Dr. Jiang if patients had started new medications that are not BB, ACEI, ARB, CBB, Statin, ASA, Nitroglycerin group
- SCID: No bipolar, no substance abuse in previous 3 months, no psychosis.
- Dr. Jiang mandated review of all recent hospitalizations, Creatinine $\leq$2.0 or GFR of $\geq$60 mL/min

These criteria were never used to screen subjects enrolled through the first three years nor were they ever formally incorporated into the protocol. It is unclear if subjects enrolled in the first portion of the trial were at greater risk because they were not screened or enrolled using this "safety criteria."

Patients Determined to be Ineligible

Four of the 25 subjects reviewed were determined to be ineligible (16%). Subject 046-116 alternated walking with a cane and using a wheelchair and did not complete the physical stress test portion of the baseline or week 6 assessments. Per protocol exclusion criteria # 5, subjects are ineligible if they are "unable to perform exercise testing." Subject 206-066 did not discontinue metprolol (beta-blocker) for screening or endpoint assessments. Per protocol exclusion criteria # 4, subjects are ineligible if they are "unable to withdrawal from anti-anginal medications during ischemic assessment phase". Subject 236-081 could not complete the physical stress test because they "walk with a cane". Per protocol exclusion criteria # 5, subjects are ineligible if they are "unable to perform exercise testing." Subject 238-082 did not hold metprolol for visit one per the coordinator note. Per the office visit that took place one day prior to visit zero, physician noted that subject was at high risk for an abdominal aortic aneurysm and had recommended an ultrasound to evaluate the issue. There was no documentation that a cardiologist approved the subject to participate in the trial. The risk for abdominal aortic aneurysm was not recorded in baseline data. Baseline line source material confirming that subject had MSIMI per protocol definition could not be found.

Documentation Regarding Diagnosis of MSIMI Missing

The protocol defines MSIMI as "1) any development of new abnormal wall motion; 2) reduction of LVEF $\geq$ 8% and/or; 3) deviation (depression or elevation) of ST-segment of ECG in 2 or more leads lasting for $\geq$ 3 consecutive beats, occurring during at least one of the 3 mental stress tasks". Source that documented that subjects met this definition was not saved in any subject files. Source for ECHOs/ECG's were found in separate file cabinets for some audit subjects, were inconsistently labeled, and are missing for certain audited subjects detailed below. There is no documentation that the wall motion abnormalities, ECHOs, or ECG's were evaluated in "real time" during the screening phase/prior to subject registration. If there is no documentation of when these procedures were evaluated, it is unclear that MSIMI (and thus eligibility) was confirmed prior to registration for all patients.

A number of "sticky notes" with the words "NO MSIMI" were found in subject files, but were not dated or signed. A review of unfiled stack of papers housed with subject files indicated that many ECHOs/LVEF values were missing. Per an undated flowchart without an identified author that was conducted after 308 potential subjects underwent baseline mental stress testing, and 127 subjects were registered for the study, 57 screened subjects were missing at least 1 EF value, and 25 registered patients were missing at least one or more EF values (18.5% of screened subjects/19.7% of registered subjects).

RCA also reviewed an instruction sheet titled "Protocol for Endpoint Reading". This sheet instructed cardiologists to re-review the week 66/visit 8 ECHO reports for each subject, fill out a score sheet for each baseline ECHO that had "never been read", fill out a score sheet for each endpoint ECHO, and fill out a score sheet if the baseline had originally been read, but the cardiologist's deviated from their initial read. Individual score sheets comparing the reads were located in some, but not all of the ECHO files.

Additionally, there were printed spreadsheets summarizing which evaluations were missing, and handwritten notes by an unidentified author with notes as to why ECGs and/or certain ECHO images could not be read (e.g. "respiratory interference, no walls seen"), and others with the note "try", presumably indicating that a cardiologist should attempt to score the images. It is unclear how or if these issues were resolved. While simultaneously endpoint evaluation by two cardiologists is explicitly discussed in the protocol, there should also be documentation that a cardiologist evaluated MSIMI at baseline in "real time" to confirm eligibility.

As previously mentioned, the source for ECHOs/ECG's was found housed separately from each patient file and it was difficult to find the reports for all subjects. The ECHO/ECG reports found for reviewed subjects were inconsistently signed off on in 2011 (between 2 months-3 years after the patients were initially enrolled). The baseline lab source worksheet/data form had a place to indicate whether or not the patient had MSIMI, and "bubble" to complete to indicate which of the three criteria qualified the subject, but this was consistently left blank across all reviewed subjects.

For subject 220-078, the ECHO report noted "suboptimal stress test due to inadequate max heart rate. Exercise induced hypotension. Target HR was not achieved due to fatigue". The subject was eligible per the initial ECHO report signed on Jan 22, 2010 because of a slight increase in wall motion from 1.0 at baseline to 1.13 during mental stress # 2. However, this report was revised by the cardiologist on May 06, 2012 to indicate that the subject had a normal motion during mental stress test # 2, thereby making the subject ineligible. The subject was eligible per the available records at the time of randomization, so this should not be considered a deviation, but the rationale for the change should be documented.

Missing Documentation of Medication Washout/Withdrawal

Exclusion criteria 4 prohibits patients from enrolling if they are "unable to withdrawal from *anti-anginal* medications during ischemic assessment phase".

The protocol further details, "All patients who will undergo the mental stress testing will have to withdraw from their *anti-ischemic* medications for 24-72 hours based upon the half-life of each medication prior to the testing, both at baseline and at the end of the 6-week treatment. Titration off anti-ischemic medications is considered necessary for assessment of the pathophysiological mechanisms of the emotional triggers of ischemia." The protocol also stipulates that there will be "careful monitoring of patients' withdrawal from *cardiac* medications".

"Anti-anginal", "Anti-ischemic", and "cardiac" medications describe a wide variety of drugs including aspirin, calcium channel blockers, beta-blockers, statins, ACE-inhibitors, and Ranolazine. Every reviewed subject in this trial did not wash out from all anti-anginal medications they were taking, and continued to take statins, aspirin, calcium channel blockers during baseline and week six assessments; only beta-blockers were withheld from reviewed subjects during the assessment periods. Per Dr. Jiang, "the grant proposal was initially drafted

in 2002 when anti-anginal or anti-ischemic medications could be considered just for Beta blockers". She further clarified holding only beta-blockers was clinically appropriate as "no physicians would be willing to hold all medications currently considered anti-ischemic medications" because it would be potentially unsafe for patients. The PI only intended to hold beta-blockers and only beta-blockers were consistently held throughout the study. Thus, RCA only included observations when it was clear that beta blockers were not held per protocol or there was no documentation of the required washouts for beta-blockers. Although RCA did not assess subject eligibility based on a more general definition of "anti-anginal" or "anti-ischemic", it is recommended that eligibility criteria be written and amended in a precise way to accurately capture washout requirements.

Subject 015-003 was on metoprolol at the time of consent/baseline. There was no documentation that the subject withdrew from Metoprolol (beta blocker) for 24-72 hours prior to screening assessments per protocol (page 17). Subject 045-018 was on anti-depressants at the time of consent. Per notes and e-mails in the file, subject was willing to discontinue Zoloft and was encouraged to contact their clinician to inform them of the discontinuation, but physician permission was not mandated by the coordinator or by Dr. Jiang. Per protocol, "Discontinuation of current antidepressants will be permitted by patients' primary care physicians or doctors who prescribed these medications to those patients." There is no documentation that this was obtained. Subject 369-119: Subject was on metoprolol at the time of consent per the medications listed in their physical exam source and completed baseline form. While it seems that subject did not take metoprolol 24-72 prior to baseline appointment, there was no definitive documentation that this was the case. Per the coordinator's notes: "Patient verified current med list, but was a poor historian and verbal history did not match Duke med history". The visit 1 note stated, "Per REMIT, pt. was asked to hold metoprolol. Pt stated that he has only taken medication sporadically over the past month".

Missing Documentation of Explicit Physician Approval

Per protocol, "Each patient's personal physician must consent to the patient being entered into this proposed study." There was no documentation that the subjects 001-001, 012-002, 015-003, 030-013, 113-034, 198-062, 206-066, and 221-073 had physician's approval to participate in the study (32% of reviewed subjects).

Overall Conclusions

RCA determined four subjects to be definitively ineligible to participate in the trial (16%), could not confirm eligibility of two additional subjects due to missing or incomplete documentation (12%), identified six subjects who were screened using additional criteria described as a 'safety checklist' that not specified in the protocol (24%), and eight subjects that did not have documented physician approval to participate in the study (32%). Overall, 21 of the 25 reviewed subjects had some issue related to trial eligibility (84%).

REMIT Recommendations

Provide a response to the IRB explaining why the 'safety screening criteria' was developed, was it was never incorporated into the protocol, and detail which range of patients were screened using this criteria. Please clarify if subjects enrolled without adhering to the "safety criteria" that was found in later subject files were put at greater risk because they were not screened or enrolled using this criteria. Any missing information required to confirm eligibility for the specific subjects in question (e.g. written physician approval to participate in trial, confirmation that beta-blockers were held, etc.) should be filed with DOCR, the IRB, and file all additional documentation in the individual subject's file.

Proactive Recommendations

Going forward, any screening criteria that potentially impact a subject's ability to safely participate in trials that would otherwise be considered trials of moderate or low risk to the subject should be formally incorporated into the protocol. Source documentation supporting a subject's eligibility be kept in the subject

file with all other subject research documentation. If source confirming eligibility cannot be kept in a subject file (e.g. a policy not to print documentation available in an EMR like Maestro Care, or a lack of space), there should be a clear note to file or accessible policy that clearly explains where eligibility source is located. With the support and endorsement of psychiatry leadership, RCA recommends that an eligibility checklist template be created within the OnCore system and its use mandated across all enrolling psychiatric IITs. Eligibility checklists should be signed by an appropriate person listed in eIRB personnel and on the delegation of authority log and include fields to indicate qualifying lab values/dates of relevant screening tests, etc. Please consider a "double-sign-off" as a quality control measure on every subject or a certain percentage of subjects)(e.g. eligibility is signed by an investigator, and then "checked" and signed off on by two different coordinators, or a coordinator and a manager).

2) OBSERVATION: DATA QUALITY

The RCA review concurs with the observations related to data quality first detailed in the QA review. Specific errors and omissions listed by subject can be referenced in appendix B, but data quality across all subjects was poor. Generally, the data practices used over the course of the trial make it difficult to fully assess protocol compliance and ensure data integrity. As was noted in the previous QA review, documentation in the trial was ALCOA non-compliant (Attributable, Legible, Contemporaneous and Complete, Original, and Accurate).

There are several sets of source worksheets/data forms used throughout the trial (December 10, 2007, v March 12, 2008, February 25th, 2009, April 15, 2009, December 09, 2009, and December 04, 2010). While it is common to amend forms throughout the life cycle of a trial, there is no clear audit trail that documents what the differences between form sets are, or when the new versions were expected to be used. Older version sets were routinely used when newer sets were available, and in a few instances, a set of forms that was version dated 6-12 months after a subject completed treatment were used. It appears that for many subjects, data were generated during treatment, but only recorded months to years later because data were often completed on forms version dated after subject completed treatment. It's unclear if data are transcribed from earlier versions of forms not found in the subject files, where original data were housed in the interim months or years, or where older sets of data are now housed if not in the subject file.

As the trial went on, it appears that additional assessments and forms were added (e.g. the Termination form, the Heart Rate Form, Psychiatric Diagnoses, Exercise Assessment, Medication Count Log), but there is no documentation to indicate when these forms are added and are expected to be used. These forms are frequently missing from subject files. In these cases, it was difficult for RCA to discern if a form was missing from a subject file, or had not been implemented when a particular subject was on treatment.

Forms were not designed to capture who completed the data or capture when data were completed. These data fields are essential in establishing a clear audit trail. Data may have been transcribed to newer sets of forms, but this was not clearly or consistently documented across subjects.

Corrections were written in purple, pink, red, green, blue, and black ink that was not always readable. Corrections were consistently not lined out, initiated, explained, or substantiated by other source. Completed items were crossed out and highlighted; the highlighter was often used for the subjective-answer surveys completed by subjects, but it was unclear if the highlighter indicated a transcription error or another unexplained issue. It is not clear how the scanner that processes the completed paper forms and populates results into the Access database interprets these corrections. It is unclear if these errors are manually corrected in the Access database.

The percentage of coronary artery stenosis was changed for subjects 001-001, 012-002, 015-003, 043-015, 045-018, 060-019, 198-062, 206-066, 301-104, 302-100, 330-111, 332-109, and 369-119 on the baseline forms, and

was either missing source that justified the change made, and/or regularly contradicted the source available in the subject file (52% of selected subjects).
Form headers that often included spaces for subject ID number, test number, date of test, etc. were often left blank. These omissions occurred in every audited subject. Because times were consistently not recorded in all mental stress tests, it's impossible to assess whether or not the tests were administered consistently across subjects (e.g. per protocol, stress tests were supposed to be 3 minutes each, with 6 minute rest intervals).

Unsigned and undated sticky notes were used consistently as essential source documentation (e.g. documentation no MSIMI). While sticky notes may be a useful tool for audit preparation and file review, they are easily separated from subject files. This is an unacceptable practice.

REMIT Recommendations

A trial specific response that provides a list of all subjects for which the stenosis percentages were changed with accompanying source documentation supporting the change should be provided to the IRB. A copy of the source documentation that supports the change should be placed in the subject's file. A response as to why so many changes were necessary across the study is also requested.

A reconciliation of all REMIT subject files should be completed. All research materials (data and source) pertaining to the same subject, should be organized in one file (e.g. SCIDs/ECHO/ECGs/submitted data). If space does not allow for this, NTFs explaining where related source can be located should be included in the subject's primary file. Whenever possible or appropriate, headers should be completed and sticky notes removed and replaced with appropriate NTFs/memos, or initialed, dated corrections on submitted data.

Please provide a response explaining discrepancies between data in the access database and data on forms and clarify if changes made directly in the access database.

Proactive Recommendations

Consider conducting and documenting training on ALCOA compliance in research for all involved faculty and staff.

All eCRFs for IITs must have a mechanism for recording who completed the forms and a field or time stamp to record when the forms were completed. Forms should also have a mechanism to indicate if and when a particular test was not performed. These mechanisms exist within the REDCap and its use should be considered.

REMIT required a large number of both contact hours and data collection for each subject. The GCP ALCOA standard should be used to help ensure reproducibility.

3) PROCEDURES AND STUDY VISITS NOT DONE/NOT PERFORMED PER PROTOCOL

Study visits and procedures were missing or not performed per protocol for the majority of subjects reviewed (23 of the 25; 92%). In most cases, the data forms created for the trial are the only source documentation, and thus, are the only way to confirm procedures are carried out per protocol. When the results for a certain procedure are left blank (e.g. standing blood pressure), there was no way to discern if the standing blood pressure was done but just not recorded on the form. If standing blood pressure was determined to be unnecessary, and thus not performed, the form was never amended to remove it.

During the 6 weeks of treatment, many subject visits required to be done in person were performed over the phone, and many phone visits were missed. Phone visits may have been considered an acceptable alternative

to an office visit, and may have allowed for increased subject flexibility, but per protocol were not permitted during certain weeks. If performing office visits over the phone was considered an acceptable substitution, then the protocol was never amended to reflect this.

The Structured Clinical Interview for DSM Disorders (SCID) assessment was not performed at baseline in seven of the 25 reviewed subjects reviewed (28%). Seven other subjects appear to have had more abbreviated SCIDs conducted (in some cases a SCID that goes through letter "J" was done, in some cases a SCID that was completed through question "F25" was done). An abbreviated version of the SCID was never IRB approved.

Not conducting SCIDs was previously reported by the study team to the IRB on October 14, 2010. Per the report the study team submitted to the IRB, "*A thorough investigation revealed that 35 of the enrolled subjects (N=100) have not had a formal SCID evaluation".* As part of the corrective action, the study team checked that additional monitoring procedures would be implemented, and commented, *"The REMIT team has had several meetings about this non-compliant issue and the research staff received education in terms of improving research compliance. The problem, i.e., not conducting the SCID, has been corrected now. Furthermore, two members of the team have been designated to periodically check data files to ensure this data is being collected from now on."* This corrective action never specified who was charged with checking data files, defined what periodically meant, or detailed how other data beyond SCIDs would be checked. There are number of unsigned and undated notes made on "REMIT checklists" in many subject files next to procedures that were not done, but it's unclear how and if the missing procedures were ever discussed or reported, and there is no further documentation related to this corrective action. There is no subject-specific or study-wide deviation logs used for the trial.

There were no LVEF and WMSI values entered for the rest periods during physical and mental stress tests for most of the audited subjects. (In looking at all REMIT subjects in the access database, LVEF values are recorded for only 10 of 400 screened subjects during the MS1 rest period). It appears from all data entered that a decision to not measure, record, and compare LVEF during each rest was made, and only baseline rest LVEFs was used as a comparator. Per protocol, "Digital acquisition of echo imaging will be obtained during the last 3 minutes of each resting period, during each mental stress test which will last for 3 minutes, and at the peak of exercise testing for 3 minutes." Based on the forms and source available in each subject's file, there is no documentation that images were consistently taken and/or measured during each rest period over the course of the trial. It is not clear if measuring WMSI and LVEF at just baseline rest and using that as the comparator was sufficient for primary endpoint evaluation as it was not the only thing required by the protocol. It's not clear how the amount of (potentially) missed ECHO images not taken/LVEF and/or WMSI measurements that were not taken affect how primary study objectives were reported on in published data.

Missed blood pressures, missing labs, missed phone visits, or missing waist measurements are minor protocol deviations when considered in isolation, however, the quantity of deviations may represent that more rigor needs to be applied going forward. With the exception of the SCID, the minor deviations that occurred frequently over a four year enrollment period with over a hundred patients were never identified or addressed by the study team during the course of study conduct. A full listing of procedures and study visits not conducted per protocol by reviewed subject is available in appendix C.

REMIT Recommendations

Please provide a response that explains why LVEF and WMSI were not consistently measured during the rest period after each mental stress test. Please explain how this is reflected or qualified in published data. A reconciliation of all REMIT subject files should be completed. All research materials (data and source) pertaining to the same subject, should be organized in one file (e.g. SCIDs/ECHO/ECGs/submitted data). If space does not allow for this, NTFs explaining where related source can be located should be included in the

subject's primary file. Whenever possible or appropriate, headers should be completed and sticky notes removed and replaced with appropriate NTFs/memos, or initialed, dated corrections on submitted data.

Proactive Recommendations

With support and endorsement from psychiatry leadership, RCA recommends that a department approved template or mechanism to log all protocol deviations be created and its use mandated across new IITs. It is recommended that the PI of each trial be required to sign off on a the log on a monthly basis, and implement corrective and preventative action as is appropriate, and amend the protocol as is appropriate. It is also recommended that study deviation logs are periodically reviewed by the management staff as well.

4) CONSENT FORMS AND PROCESS

One hundred and thirty-four informed consent forms were reviewed. Seventeen of the consents reviewed had at least one issue (12.7%). There were a wide variety of consent issues that constituted multiple violations of federal regulations, Good Clinical Practice (GCP), and DUHS IRB policy.

As was reported in the May 03, 2018 QA review of the REMIT trial, the signed informed consent do not consistently have two subject identifiers entered. Per Duke policy, Duke subjects should have their name and medical record number entered on the upper right hand corner of every page of the consent.

No person obtaining consent (POC) signatures were completed for subject 052-000 for the REMIT trial, and no POC signed subject's 221-073's REMIT or REMIT repository consent.

As was identified in the May 3rd, 2018 QA review, it was difficult to determine if the POC that signed the consent was appropriate because the signature was not readable and could not be compared against signatures on the DOA for subjects 001-001, 113-034, 206-066, and 220-078.

A number of subjects signed an incorrect and/or unapproved version of the REMIT consent. They are listed in the table below:

Subject Number	Date of Consent Used	Version date of Consent Approved at the time of registration
049-020	July 05, 2007	August 15, 2007
099-000	March 7th, 2008	August 11, 2008
100-027	March 7th, 2008	August 11, 2008
101-028	March 7th, 2008	August 11, 2008
102-029	March 7th, 2008	August 11, 2008
105-031	August 12, 2008	August 11, 2008
109-033	August 12, 2008	August 11, 2008
113-034	August 12, 2008	August 11, 2008
198-062	August 12, 2008	August 11, 2008
206-066	August 12, 2008	August 11, 2008

It is unclear that the trial was ever discussed with the subject/informed consent process was carried out appropriately for subject 220-078. From notes in the subject's file, it appears that subject canceled their visit, and faxed a signed consent back to the office.

A blank consent document with an unsigned, undated "sticky" note saying "patient left copy behind" is in subject's 238-082. There were no documented efforts to return the subject's copy of the consent to them during the course of the trial.

A consent for the REMIT repository trial was missing for subject 064-000.

REMIT Recommendations

Report the missing consent for subject 064-000 to the IRB. Generate a NTF to include in the subject file that indicates the original consent could not be found, and the incident was reported to the IRB.

Attempts to obtain signatures from anyone employed at Duke for the REMIT DOA log should be made. Generate a NTF for any signatures that cannot be obtained.

Proactive Recommendations:

With support and endorsement from psychiatry leadership, RCA recommends a DOA log template be designed and its use mandated for all pending and currently enrolling psychiatry IITs.

Establish a system to ensure that study team members have limited or qualified access to previous versions of the consent or are specially trained to only use current-IRB approved version of the consent.

Consider a formalized training for faculty and staff on the logistics and importance of the informed consent process.

5) PATIENTS ENROLLED ON REPOSITORY TRIAL DURING 8 MONTH LAPSE OF IRB APPROVAL WERE NEVER INFORMED OR RECONSENTED

Per federal regulation and GCP, the IRB is required to provide a continuing review of human subject studies at least once a year. IRB approval for the REMIT repository trial expired from February 3rd, 2008 to September 9th, 2008. Thirty-four patients were enrolled to the repository trial during this time, on an expired consent. This issue was appropriately reported to the IRB in fall 2008. In the corrective action, the IRB mandated that a letter be sent to each of the subject's consented during the lapse with a request for them to re-consent. There is no documentation that the study team followed the IRB directive or that this group of patients were ever notified or re-consented.

REMIT Recommendation

Consult the IRB if it is permissible to use these subject samples or whether existing samples should be destroyed. If the samples have already been analyzed, work with the IRB to determine if collaborators should be notified of the lapsed approval and failure to notify patients, and advised to destroy samples. Consult the IRB to determine if subjects should be notified of the lapsed approval and re-consented.

6) OBSERVATION: SAFETY REVIEW FOR FIRST 20 PATIENTS PERFORMED

An e-mail in the correspondence section of the regulatory binder indicated that a safety review would be submitted after the first 20 patients were enrolled. Per the PI, "this particular request came from concern of safety on performing mental stress testing on IHD patients". No documentation that this review was ever done or reviewed by the IRB could be located.

REMIT Recommendation

Provide additional documentation including all IRB correspondence and directives regarding the safety review. Clarify if the request was made as part of the IRB initial review and approval.

7) OBSERVATION: DRUG ACCOUNTABILITY ISSUES

Records in subject files explicitly indicate that drug was mailed for subjects 043-015, 109-033, 113-034, and 236-081, 302-100, 342-112, 301-104, 332-109, 330-111, and 399-127. Because subjects 015-003, 046-116, 045-018, 198-062, 238-082 missed office visits where they were to receive drug, but took drug per medication count logs in the file, it appears that drug was mailed. The protocol does not permit drug dispensing by mail, and the IRB did not approve drug dispensation by mail separately. In the response to the previous QA review, Dr. Jiang wrote, "The protocol of REMIT was that participants picked up the study medication at one of our offices".

As was previously noted in the QA review of the REMIT trial, drug reconciliation was not performed and/or documented consistently across subjects. Medication count logs were not located for 001-001, 012-002, 043-015, 060-019, 109-033, and 198-062, and 220-078. Medication order forms and drug tapering worksheets were inconsistently used or incompletely filled out across all subjects.

A drug diary/instruction sheet was in subject files 030-013, 045-018, 046-116, 301-104, 332-109, 330-111, 342-112 and 399-127, but was never approved for use by the IRB.

The medication count log for subjects 030-013 and 238-082 indicate that much more medication was returned than should have been, and subjects were non-compliant with study medication. There are no notes indicating that subject non-compliance was discussed.

A note on a drug order form in investigational pharmacy files indicates that drug for subject 105-031 was re-dispensed because the [original] "drug [was] lost in the mail". This was never reported to the IRB and drug was never found or reconciled.

Study kit numbers were consistently not completed on the medication count forms.

REMIT Recommendations

The drug that was lost in the mail should now be reported to the IRB. Please provide details on how drug reconciliation and drug destruction was carried out for the REMIT trial. Please include information on who was responsible for performing pill counts, who was responsible for completing the medication count form. Please detail where medication was expected to be stored and describe how unused medication was destroyed.

Proactive Recommendations

All drug diaries instructing subjects how to take medication must be approved by the IRB. For trials that involve oral drugs with specific tapering instructions, consider using a diary designed for subjects to record days/times they took their medication to better track subject compliance. If the study team, as opposed to the Investigational Drug Services, is responsible for any portion of drug accountability (e.g., counting returned drug and tracking unused medication, recording this on a medication log, destroying returned drug), the trial should have an established written drug accountability plan, either in the protocol or a pharmacy manual.

8) OBSERVATION: DOCUMENTATION OF DSMB REVIEW AND APPROVAL INADEQUATE

Records pertaining to the Data and Safety Monitoring Board (DSMB) required for this trial are missing and/or incomplete. Per the protocol:

"The DSMB will review trial protocol so that the members may become fully apprised of the study design and procedures. For monitoring purposes, a DSMB report will be prepared yearly for the trial. It will be the responsibility of the trial statistician to prepare and submit this report. Data will be provided in a blinded fashion, unless otherwise specified by the DSMB. If disclosure of the treatment conditions is required, an independent statistical analyst will be asked to prepare this section of the DSMB report. After each meeting, the DSMB Chair will submit a written summary to the study PIs. This document will summarize the following for each protocol evaluated during the meeting: (1) judgments as to whether participants' safety, privacy, and confidentiality has been consistently assured by the investigators; (2) recommendation for any interim analyses pertinent to evaluating participants' safety; (3) judgments as to whether research instruments have been administered in a uniform manner and in a way that maintains participants' confidentiality; (4) review of the study's progress toward recruitment goals, quality of data, treatment plan adherence, and participant retention/attrition rates; (5) review of new scientific literature pertinent to the safety of participants or the ethics of research participation; (6) decisions as to whether risk/benefit ratios have changed to the extent that the trial should be modified or discontinued".

The DSMB correspondence does not meet the specific requirements established in the protocol. There is no documentation that quality of data or treatment plan adherence was discussed by the DSMB over the course of the trial.

It is not clear what data was prepared for or reviewed at the June 2008, June 2009, and June 2010 meetings. There are no detailed minutes detailing the information above for any year the DSMB met, although there are meeting minutes for the June 2010 meeting that address some of the topics mentioned above.
Brief letters authored by the DSMB Chair after each meeting approve the study to continue enrollment were on file. The June 2008 letter requested that a DSMB charter be approved and requested additional data tables. It's not clear if these additional tables were ever provided. There is a draft version of a DSMB charter in the electronic files, but there's no documentation that it was ever approved or referenced thereafter. The DSMB letter that approved continued enrollment on the study after the June 2009 meeting was dated February 12, 2010, approximately eight months after the DSMB meeting took place. The July 2010 DSMB letter approved an increase in the sample size. A detailed report dated December 2010 and referencing a January DSMB 2011 meeting date was found in the file, but no records that a January 2011 DSMB meeting, or any final DSMB meeting took place was located. Trial enrollment continued through August 2011.

This protocol had particularly specific language regarding the required DSMB summary, and while there were general letters documenting that the DSMB met and determined the trial was safe to continue enrollment, there is insufficient documentation as to what was prepared for review and exactly what was reviewed and discussed by the committee. The committee was charged with reviewing both treatment plan adherence and quality of data; based on the RCA review, both protocol adherence and quality of data became issues in this trial, and it's unknown if this was ever brought to the DSMB attention or discussed by the DSMB. It is also concerning that the letter permitting enrollment after the June 2009 DSMB meeting was issued on February 12, 2010; fifty-five subjects were consented during that time period.

REMIT Recommendations

File in the regulatory binders all additional documentation provided by the external DSMB and all materials and/or minutes generated before or after the REMIT DSMB meetings. Generate a NTF explaining that permission to continue enrollment was granted verbally at the June 2009 DSMB meeting and the study team continued enrollment based on that.

Proactive Recommendations

Outline the existing internal Psychiatry procedure for determining trials that require DSMBs and how members are appointed and approved. Include detailed language regarding DSMB membership, expectations and procedures in a DSMB charter, instead of new study protocols. A draft charter should be provided to (and potentially revised by) external DSMB members to clarify their obligations prior to any subject enrollment.

9) MISSING, INCOMPLETE, AND/OR INACCURATE REGULATORY BINDERS

Generally, the multiple paper and electronic binders kept for the REMIT trial were poorly organized, and there was almost no required regulatory documentation filed for the REMIT repository trial. There were five paper binders for the REMIT trial and a small portion of one of the binders dedicated to repository trial.

The REMIT trial was initially IRB approved in 2006, and is currently open with the IRB. During the course of both trials, regulatory approvals and regulatory documentation were stored electronically, but there are no accurate NTFs that explain when this transition occurred. There was a memo in the REMIT regulatory binder # 1 that said "versions of the protocol submitted during and after 2007 are in the shared drive", but this was not accurate. Some regulatory documentation before and after 2007 are in the paper files, and some are in the electronic files. The paper binders were divided into tabs, but the paperwork was not consistently stored according to type of documentation or type of approval. Regulatory files were also stored in a number of different areas on the shared drive REMIT folder, and it was not always intuitive as to where to locate a specific document.

The majority of amendments for this study pertained to key personnel changes, but no IRB letters that approved only key personnel changes were filed in the paper binder or electronically. Progress reports prepared for continuing reviews, and protocols documents approved during continuing reviews were regularly filed, but the continuing review approval letters were consistently missing.

The DOA Log for the REMIT trial was incomplete and insufficient. As reported in the initial psychiatry QA review there was no documentation that a DOA was created at the time of initial IRB approval (August 17, 2006). There is an "effective date of August 09, 2006", but it not clear when this DOA was completed (reportedly created by [redacted] in December 2017).

There is not space on then template for PI log sign off/signature. The PI had initialed the one existing version of the log in the binder but there is no documentation that she reviewed or initialed changes over the course of the study. There is no space for signature date of the log template, so it in unclear when Dr. Jiang signed the existing log. Page numbers at the top of the log are not completed appropriately, and the great majority of personnel have not signed the DOA log. There are a number of personnel whose start and stop dates contradict what it listed in the eIRB. A full listing of the DOA discrepancies are available in the table in appendix D.

A separate DOA log was never kept for the REMIT repository trial, as is required. There were no IRB approved documents or IRB approvals for the initial approval of the REMIT repository, for any amendments, or continuing reviews.

Overall, the REMIT regulatory binder was missing copies of IRB approvals for any key personnel changes and continuing reviews. IRB approval letters and IRB approved documents for the REMIT trial that were not filed appropriately are fully detailed in the table available in appendix E.

REMIT Recommendations

Perform complete reconciliation of the REMIT and REMIT Repository regulatory binders. Documents housed within the "Regulatory Binder" and "REMIT Audit" files should be consolidated into one electronic regulatory binder that includes electronic copies of everything in the paper binders. The paper binder should be archived except for documents requiring a wet-ink signature. If missing or incomplete documents in appendix II are found, file in the electronic binder. Generate NTFs for curricula vitae (CVs), licenses, Collaborative Institutional Training Initiative (CITI) trainings and signatures that cannot be obtained for anyone listed on the DOA or in the eIRB. Resolve date discrepancies between eIRB and the DOA log. Anyone listed on one document but not the other should now be added.

Proactive Recommendations

Develop a standard DOA log template and mandate use across all pending and enrolling Psychiatry IITs. Develop a standard but customizable electronic regulatory binder folder for all pending Psychiatry IITs.

10) OBSERVATION: RESEARCH DATA SECURITY PLAN INCOMPLETE AND NOT CREATED IN A TIMELY MANNER

Per Duke policy, all non-exempt approved open trials must have an approved Research Data Security Plan (RDSP) on file. The RDSP for this trial appears to have been created in May 2018 after the CRU review, but is not dated. The access database where published data are housed is not mentioned in the RDSP. The plan does not specify how access to the electronic database are limited and/or controlled. The RDSP also mentions that Cardiac RN will be in the room during stress test. Through the life cycle of the trial, the protocol consistently stated "procedures for protection of subjects against potential risks include attendance of a cardiologist at all mental stress and exercise testing and careful monitoring of patients' withdrawal from cardiac medications with 24-hour on call". This detail is inaccurate, and does not seem appropriate for a RDSP.

The RDSP requirement was implemented for new trials in November 2011, after enrollment to this study had closed. A retrospective survey in REDCap was administered by Duke Office of Clinical Research (DOCR) to all existing approved, non-exempt studies at that time, but documentation that one was requested or completed for this study could not be located.

REMIT Recommendations

Revise the REMIT RDSP and include information regarding paper source document worksheets used as scanned data forms. Specify in the RDSP how access to the electronic database is limited and controlled. Delete information about who needs to be present during testing.

Proactive Recommendations

Consider providing RDSP training for future study teams. Consider providing training on writing RDSPs to staff who will routinely do so.

11) VIOLATION OF THE DUKE UNIVERSITY SOCIAL SECURITY NUMBER USAGE POLICY

Social security numbers were found in files for subjects 109-033, 206-066, 221-073, 220-078, and 238-082. There were copies of 28 Duke University Health Systems' Accounts Payable Check Requests with patient names and social security numbers in a miscellaneous, unfiled stack of papers. There was a list of subjects' demographic information and associated social security numbers in a miscellaneous, unfiled stack of papers (16 pages total). A spreadsheet labeled "all chf patients" had social security numbers listed for some patients (17 pages total). There is an additional spreadsheet labeled "Patient Contact Spreadsheet" with social security numbers found. The names listed do not appear to be connected to the REMIT trial in any way.

REMIT Recommendation:

Follow recommendation of the OARC Privacy unit assessment to be performed subsequent to the RCA review.

Proactive Recommendations:

If relevant to future studies, ensure teams review the Duke SSN Usage Policy.

12) DUKE EMPLOYEE ENROLLED WITHOUT REQUIRED IRB APPROVAL; RECRUITMENT OF STUDENTS, EMPLOYEES, FRIENDS, AND FAMILY MEMBERS AS RESEARCH PARTICIPANTS NOT FOLLOWED

Subject 220-078 was a Duke University employee consented on October 1, 2009. There was no IRB approval that allowed employees to participate in the REMIT trial as required by the DUHS' Human Research Protection Program (HRPP) policy "Recruitment of Students, Employees, Friends, and Family Members as Research Participants". The current version of the policy can be referenced on the DUHS IRB website; the March 14, 2008 version was in place at the time the subject was enrolled.

REMIT Recommendation

Please report this incident to the IRB. It is recommended that the PI and current team study team members confirm in writing that they have reviewed the policy cited above as part of the required response.

13) ADVERSE EVENTS NOT REPORTED CORRECTLY

In the follow-up form completed for patient 302-100, a note indicates that a cardiac cath was done on October 29th, 2010 after patient had pneumonia. The dates the subject had pneumonia were not reported on adverse event forms, and it's unclear when the pneumonia occurred. The subject was randomized on October 22nd, 2010 and completed week 6/visit 8 assessments on December 09, 2010. Pneumonia was not reported while the subject was being treated, although the cath was done during treatment. It should be clarified when the subject had pneumonia, and a Serious Adverse Event (SAE) reported as necessary.

Subject 342-112 reported nausea as recorded in the coordinator's notes, but this was not captured on the AE form.

REMIT Recommendation

Investigate if and how subject 302-100 had pneumonia while on trial and amend adverse event forms and/or file a SAE report accordingly. Amend subject 342-112's adverse event reporting to include nausea.

14) PROTOCOL INCORRECTLY SPECIFIES THAT [redacted] WILL PERFORMED ALL ECHOCARDIOGRAMS

The currently approved protocol specifies that [redacted] perform all ECHOs for study subjects in his laboratory. For the great majority of study subjects, [redacted] had no involvement, and thus, there are hundreds of unnecessary protocol deviations when ECHOs were performed by any other study member. Per Dr. Jiang, [redacted] was not able to comply with the protocol, and other cardiologists were then used. [redacted] compliance issues were not documented in any trial records reviewed by RCA. Per IRB records, he was removed from key personnel on June 29, 2009, but the protocol was never amended to remove reference to him.

REMIT Recommendation

It is recommended that a response detailing [redacted]' non-compliance be provided. It is recommended that the protocol be amended to remove reference to [redacted].

15) LOST SAMPLES FOR THREE REPOSITORY SUBJECTS

Correspondence in the REMIT repository regulatory binder indicated that three tubes of blood were lost for a repository subject. No documentation that this was reported to the IRB could be located.

REMIT Recommendation

Please report the three lost tubes of blood to the IRB for the repository subject.

APPENDICES

Appendix B: Observation 2, Data Quality Issues by Subject

Subject Number	Data Issues
015-003	The screening/baseline visit for patient 015-003 occurred on October 05, 2007, but the forms used are March 12th, 2008. The week 6 visit took place on December 05, 2007, but data from this visit were completed with March 12th, 2008. It is not clear where data were housed in the interim. Some of the information captured on this form is not available in any other source documentation.
	The subject identification number on the baseline arithmetic test in subject 015-003's file is left blank. It could not be confirmed that this assessment applied to this patient.
	The baseline wall segment scoring is incomplete for patient 015-003.
	A stack of completed forms with a pink "sticky" note labeled "OLD FORMS" was found in the file. Forms for subject's ID 016000 was in subject's 015-003's subject file. A stack of forms for 015-003's has a "sticky note" with the "Forms recopied April 08, 2008".
	The LVEF % was left blank on the source ECHO report, but is listed as 56% on the form, and in the access database. No source data was located to confirm data entered for LVEF % endpoint assessments.
	The baseline percentage has a RCA % of 80%. This appears to match source. 80% was crossed out, and 25% was replaced, but it is not signed, initialed, or explained.
030-013	Although the baseline visit was performed on December 17, 2007, form versions were labeled March 12, 2008. It's unclear where data were housed in the interim. There were a few forms paper clipped together with a "sticky note" labeled "old forms!", but it is not certain if data from these forms were transcribed into the later versions. Visit 0 is listed as December 17, 2007, December 17, 2008, and June 04, 2008 on three different forms. The coronary artery assessment percentages were changed in red pens without initials or dates, and the supporting source referenced is not in the subject's chart. No resting EF is recorded at baseline. Throughout subject chart, subject identifiers are partially completed and not lined out and initialed. The wall segment scoring sheet is not completed for the W6/V8. An exercise assessment forms with a "Visit 1" date of 03May2010was completed > 2 years after the subject finished treatment, and appears to have been completed as part of the follow-up phone call.
046-116	Errors on forms are marked with a highlighter and not lined out or initialed.
	The phone interview box is left blank on V0.
	A set of forms is paper clipped together with a sticky note "recopied forms-do not use!"
	There are no end times listed on the baseline stress test instructions, no start time on the arithmetic test, no start or end times completed on the speech tests.
	An exercise assessment form completed with a date years after subject completed treatment is in the file, and appears to have been done as part of FU.
045-018	There was no source included to support the stenosis percentages entered under the coronary artery assessment.
	The additional medication form was not completed after the subject reported taking Allegra during the visit 1 phone call (23April2008).

	The Hostility assessment scale was completed twice and no start and end times were entered on the mental stress test forms.
	The exercise assessment form was completed in May 2010, well after the subject completed treatment, as part of the follow-up.
198-062	The December 10th, 2007 version of forms were used when updated forms (v March 12, 2008) were available.
	Subject identification was left completely blank on the BDI assessment. There is no way to confirm that the baseline BDI was completed by this patient.
	The stenosis percentage had been changed in red pen, not dated or initialed, and do not match source documents.
	Certain forms were completed using "draft" versions of the forms
	Subject ID was not completed on the baseline mental stress test and public speech tests. It could not be confirmed that the forms in the file reflect this subject's results
	Some forms in subject 198-062's chart were labeled with Screening ID 198000.
	There were no start/end times on the stress test instructions, no start times or completion notes on the mental arithmetic test, no start time or completion notes recorded for the mirror trace test, and no start or stop times for the speech test.
	The wall segment scorning and drug tapering worksheets are in the file, but left completely blank. Wall segment scoring data are not entered into access.
238-082	Results of the coronary artery stenosis assessment percentage were changed on the baseline form without a line-out, initials, or explanation in red pen. The changes made do not match values in source documentation.
	Errors/changes made on the baseline lab form are highlighted, instead of cross-out, dated, and initialed.
	For baseline, the subject ID number was left blank on the stress testing instructions, and the time was left blank. The start time on the baseline arithmetic test was not recorded. A blank baseline mirror test form was in the subject file. The end time and test # were not recorded on the speech test.
	The W6 wall segment score form was left blank, with a "sticky note" attached indicating that results had already been scanned. It is unclear when/if segment scoring was completed. These values are blank in the access database, and source data for both baseline and W6/Visit 8 data could not be located to be compared.
	The W6 mental arithmetic stress test start time was not recorded. There is no start time recorded on the mirror trace test, and no start and end times recorded on the speech test. Both the arithmetic and speech tests are labeled "test # 8".
	The W6 adverse event form reports no outcomes. This contradicts earlier reported events of a "low libido", and being "emotionally flat".
Subject 302-100	The SCID cover sheet was not completely filled out.
	Baseline wall segment form is noted is as "missing" on the REMIT checklist, but is in the subject file and partially completed. There is only 1 set of resting data, and resting values before mental stress test I, II, and II, and the physical stress tests are not recorded. (MOST subjects just had 1 resting baseline, not between each test).
	Coronary artery stenosis percentage was changed from 100% to 25% with an accompanying note that said, "OKed by Jan 11/29/11". The percentage change contradicts the source in subject file.

	Baseline wall segment scoring data does not match source exactly and the discrepancies are not explained, signed, or dated.
	There are no wall segment scoring week 6/visit 8 data.
	There is no start/stop times completed for the stress test instructions, and no start times completed for the arithmetic test, the mirror test, or the speech test.
301-104	There are no start and end times for the mental stress tests performed at baseline and week 6.
	There are no LVEF values entered on the baseline form.
	While the subject reported no adverse events, the adverse event form is left blank; a note should be added to this form indicating that no events were reported.
	Sticky note with subject ID is added to certain forms, and the subject identifier is left blank on the form.
	The week 6 wall segment scoring form is completely blank.
Subject 332-109	The stenosis percentages entered under the coronary artery assessments are not supported by the source in the subject's files.
	There are no start and end times on the mental stress tests at baseline or week 6.
	The week 6 wall segment scoring form is completely blank.
330-111	The stenosis percentages have been changed on the coronary artery assessment form, but this change is not supported by any included source documentation.
	Mistakes and errors are noted with a highlighter on all subject's forms.
	There are no start and end times on all mental stress tests.
342-112	The SCID check on the cover sheet was not completed.
	The REMIT checklist indicated that there was a no baseline wall segment scoring form, but an incomplete form was located. The incomplete form was missing values for mental stress I, II, and III rest periods, and for the physical stress rest period.
	No start and end times were completed on the baseline stress test instructions. No test numbers or start times were completed on the baseline arithmetic test, mirror trace, or speech tests.
	The week 6/visit 8 wall segment scoring form was completely blank.
	Mistakes on multiple subject forms were corrected with a highlighter, not lined-out initialed, or dated.
	Beginning and end times were not recorded for stress test instructions or the speech test. The arithmetic test is not labeled with a number, and the start time is not entered. The mirror trace test start time is not entered
369-119	The same form are partially completed in both blue and black ink throughout the subject's file.
	There are no start and end times recorded for the mental stress tests performed at baseline or week 6.
	Mistakes or errors on subject surveys are highlighted. It is unclear if subject checked two answers, or if the highlighter indicates things were transcribed incorrectly.

	The stenosis percentages for the coronary artery assessment was changed without date or signature and contradicts the source included in the subject's file. While the subject reported no adverse events, "none" should have been entered on adverse event forms; the forms should not be left blank.
	The "change in cardiac drug form is missing the start date for the new medication (Diovan), and the stop date for the old medication (Avapro). It was reported in the coordinator's note that subject was not taking metoprolol anymore, but this was not included on any change of medication form.
	The week 6 wall segment form was completely blank.
Subject 399-127	The baseline start and end times were not completed on stress test instructions. The test numbers and start times were not completed on all mental stress baseline tests.
	The additional medication form was not completed although subject was on OxyContin after arm fracture.
	The wall segment score was not completed on the week 6/visit 8 form.
	No data on LVEF were recorded at baseline on form. Baseline ECHO report was found in a separate file, and confirmed that patient was eligible, but this data are missing from the forms in the subject file; data is entered in the access database. Baseline wall segment scoring on the form in the subject's file does not match source.

Appendix C: Observation 3, Procedures and Study Visits Not Conducted Per Protocol by Subject

Subject Number	Procedures/Study Visits Not Done Per Protocol
001-001	The week 4 phone visit was not done. Waist measurements at baseline and W6 were not done.
012-002	The week 4 phone visit was not done.
015-003	Week 0/visit 3 occurred via a phone call, not office visit, as required per protocol. Vital signs were missing. It is not clear if medication was mailed to the subject. RVSP, HBA1C, and troponin values are missing from the form and appear to have not been drawn. The week 2, week 4, and week 5 phone call visits were not done. Standing vitals were not done at week 6 visit. No waist measurement was done during week 3 visit (December 05, 2007).
030-013	Respiration rate, RV est pressure, LDL, CK, troponin and BNP were not done during Screening visit. Respiration rate not done at week 3/visit5. It is noted that the subject "opted" for a one month prescription for Lexapro instead of the drug taper procedure described in the protocol. There is nothing in the protocol to indicate that this is permitted.
043-015	Vitals were not done at the randomization visit.
060-019	Blood pressure at screening was not done. Waist measurements at week 3 were not done.
045-018	Baseline blood pressure not taken per protocol. Week 0/visit 2 appears to have been done over the phone. The respiration rate is missing on the week 6/visit 8 and standing vitals were not done.
046-016	Blood pressures not taken during required times during the baseline rest period, and then taken at 20:45, 22:45, and 23:45. There appear to have been no labs drawn at baseline. The week 0/visit 22 was performed by phone, when protocol requires an office visit, and vitals were not performed. Respiration rate was not done at week 3/visit 5. Blood pressure not taken per protocol due to the need to reposition subject at week 6/visit 8.
109-033	The week 1 and week 5 phone visits were not done; the subject could not be reached. Week 3 was completed as a phone call when the protocol called for an office visit.
198-062	BP, HR, and waist measurements were not done at baseline. BNP and troponin were not assessed at baseline. BP and HR were not taken during MS exam II. Platelets were drawn per protocol, but could not be processed by the lab because the lab was closed. Vital signs were not done during week 0 /visit 2. Week 3/visit 5 appears to have been done via phone call, and not office visit, as is required by protocol. It appears that medication was mailed to patient. BP and HR were not done at all required times during physical stress testing and mental stress II. No documentation that the baseline Structured Clinical Interview for DSM Disorders (SCID) was conducted could be located.
206-066	There was no documentation that a SCID was done at baseline. The randomization and week 3 visits were completed as phone calls, and not office visits as required by the protocol.
221-073	There was no documentation that a SCID was done at baseline. No vitals were done at screening.
220-078	There was no documentation that a SCID was done at baseline.
236-081	There was no documentation that a SCID was done at baseline.

238-082	CK, CK-MB, Troponin, and BNP were not done at baseline. The randomization visit was completed via phone call when the protocol requires an office visit. Vital signs were not done, and concomitant medication information was not collected. There was no note to indicate how the subject received drug, implying the subject was mailed drug. The week 3/visit 5 was done via phone call when the protocol required an office visit. Subject height, weight, and vitals were recorded, but there is no note confirming that they were done by the subject at home. Vitals were not performed at the week 6 visit. BP was only recorded at: 45, 2:45, and 4:45 of the physical stress testing. Source could not been found for subject's baseline and week 6/visit 8 ECHOs. The subject's SCID was not conducted at baseline and was performed during the week 6 visit. It appears to be an abbreviated version of the SCIDs conducted for other subjects.
302-100	Baseline HbA1C, CK, CK-MB, troponin, and BNP were not done. The week 0/visit 2 was completed by phone, when an office visit is required per protocol. Concomitant medication information was not collected. Per note, this was completed by mail. Week 2/visit 4, to be completed by phone), was missing. Week 3/visit 5 was completed by phone when an office visit was required. Subject was mailed medication. The subject failed to hold his beta-blocker for the week 6/visit 8 assessments.
313-101	There was no documentation that a SCID was done at baseline. The randomization visit was completed as a phone visit and not done as an office visit per protocol. Standing BP was not done at screening or week 6.
301-104	The SCID done appears to be an abbreviated version that the more complete one done for other audited subjects. CK, troponin, BNP were not done at baseline. Baseline blood pressure not taken per protocol. The week 3/visit 5 was done by phone. It was noted that the subject's vitals were obtained from [redacted] at [redacted]". It does not appear that she was ever added to the DOA, or authorized to share information collected for research. There were no standing vitals collected. The BDI was not completed during week 6/visit 8. No standing vitals or BP during the W6/V8 physical stress tests were completed.
332-109	The SCID done appears to be an abbreviated version that the more complete one done for other audited subjects. BNP was not done at baseline. BP during baseline not completed per protocol. The week 3/visit 5 was completed by phone, and only sitting vitals were reported by the subject. The week 6/visit 8 BDI was not completed, there were no standing vitals, and BP was taken once during physical stress test.
330-111	The SCID done appears to be an abbreviated version that the more complete one done for other audited subjects. CK and BNP were not done at baseline. The week 0/visit 2 was done by phone, and there were no vitals collected. Week 2/visit 4 4, Week 3/visit 5, Week 4/visit6, and week 5/visit 7 were not done. There were no standing vitals done week 6/visit 8.
342-112	The SCID done appears to be an abbreviated version that the more complete one done for other audited subjects. The week 0visit 2 was completed by phone, when completed by phone, when an office visit is required per protocol. No vitals were done and concomitant medication information was not recorded. Week 3/visit 5 was completed by phone, when an office visit is required per protocol. No vitals were done. Medication was mailed. Medical history was not collected at week 6/visit 8.
369-119	The SCID done appears to be an abbreviated version that the more complete one done for other audited subjects. Week 0/visit 2 appears to have been completed by phone, and no vitals were done. Week 2/visit 4 phone call was not done.

Appendix D: Observation 9, Delegation of Authority (DOA) Errors, Discrepancies with eIRB

Personnel Name	Discrepancy Detail
[redacted]	The DOA lists start date as September 8th, 2006. Start date in eIRB is September 06th, 2007.
[redacted]	eIRB lists her start date as May 4th, 2017, but she is added, added to DOA with a March 31, 2017 start date.
[redacted]	Listed as Study Coordinator in the eIRB with a start date of August 14th, 2006 6, but is not listed on the DOA.
[redacted]	Listed as a Co-Investigator with a start date of August 14, 2006 6, but is not listed on the DOA.
[redacted]	Responsibilities were not completed on the DOA.
[redacted]	Listed with a start date of September 08th, 2006 on the DOA. Start date in eIRB is September 06th, 2007.
Wei Jiang	Listed in DOA with start date of September 08th, 2006.
[redacted]	Start date in eIRB is September 06th, 2007, but start date on DOA is August 14th, 2008.
[redacted]	Listed as a Medical Resident on DOA with a start date of June 03rd, 2011, and an end date of June 19th, 2012. Not registered in eIRB.
[redacted]	Start date on the DOA September 08th, 2006. Start date in eIRB July 20th, 2010.
[redacted]	Listed in eIRB with end date of September 06th, 2007. Not on the DOA.
[redacted]	Listed as a Co-Investigator with a start date of May 06th, 2008 in eIRB, but with a start date of September 08th, 2008 on the DOA.
[redacted]	Listed as a collaborator on the DOA with a start date of September 8th, 2006. Start date in eIRB of May 12th, 2010.
[redacted]	Listed as a Co-Investigator with a start date of September 08th, 2006 on the DOA, but a start date of May 6th, 2008 in eIRB.
[redacted]	Start date of September 8th, 2006 on the DOA. Start date of January 25th, 2008 in eIRB.
[redacted]	Not listed on the DOA log. Start date in eIRB January 25th, 2008.

Appendix E: Observation 9, Missing and/or Incomplete Regulatory Documentation for REMIT Trial

Date of IRB Notification / Approval	Type of Document or Approval	IRB Number/ Activity Number	Detailed Document Description	Comments
17Aug 2006	Initial Approval	89608	-	A copy of a clean, IRB approved protocol could not be located. A "tracked-changes" version was found.
09Feb 2007	Amendment	96631	Protocol changes; addition of a questionnaire, use of ECHO over RNV.	A clean, approved copy of the applicable research summary could not be located. A "tracked changes" January 29th, 2007 was found.
07Mar 2007	Amendment	98625	Drug used changed from sertaline to escitalopram in ICF and protocol.	A clean copy of the approved protocol could not be found. The approval letter, and approved research summary, and a "tracked changes" protocol were filed.
05Jul2007(the approval date is unclear on copy provided by	Recruitment Materials	94187	Approval of newspaper ad	This was not found in either the paper or electronic binders.

Paper host)				
27Jul2007	Recruitment Materials	94036	Approval of study information card/recruitment material.	This was not found in either the paper or electronic binders.
30Jul2007	Continuing Review	No identification number for continuing reviews in paperhost.		The applicable protocol and model ICF were found, but the continuing approval letter was not.
16Aug 2007	Amendment	94173	Correction of inconsistent drug tapering language between ICF and protocol.	Page 7 of the approved model consent was in the paper binder, but all other pages were missing. All other approval materials were filed appropriately.
06Sep 2007	Amendment	101848	Removal of [redacted], add of [redacted] and [redacted] as research assistants.	No IRB approval of the key personnel changes were filed.
09Oct 2007	Amendment	104074	Revisions to protocol eligibility criteria.	The research summary associated with this approval was not found. All other documentation was filed on the server, or in the paper binder.
08Jul2008	Revised Key Personnel	106753	Add of [redacted] as research assistants, and removal of [redacted]. Study roles changed for [redacted], and [redacted] from Co-I to sub-I.	IRB approvals of key personnel changes were not filed in paper binders or electronically.

12Oct 2008	Continuing Review	CR1		Progress reports applicable to this review, and correspondence regarding a delayed re-approval are filed, but the continuing review approval letter could not be located.
15Aug 2008	Amendment	AMD1	Revised key personnel	No IRB approvals of the key personnel changes were filed.
20Oct 2008	Amendment	AMD2	Elimination of BDI inclusion criteria.	The associated protocol was filed, but the IRB approval letter was missing.
13Nov2008	Amendment	AMD3	Addition of GWBS.	Tracked and clean copies of the protocol were filed, but the IRB approval letter is not filed.
29Jun 2009	AMENDMENT	AMD4	[redacted] and [redacted] were added and [redacted] and [redacted] were removed from study personnel.	No IRB approvals of the key personnel changes were filed.
24Jul2009	CONTINUING REVIEW	CR3		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
13Nov2009	AMENDMENT	AMD5	Study Personnel Change to add [redacted] and remove [redacted]	No IRB approvals of the key personnel changes were filed.
25Feb 2010	AMENDMENT	AMD6	Exercise Assessment Questionnaire	No IRB approvals of the key personnel changes were filed.
3/2/2010	AMENDMENT	AMD7	DSMB Report June 16, 2009	The report was filed electronically, but IRB acknowledgement/approval of the report was not filed.
5/2/2010	AMENDMENT	AMD8	Study Personnel Change adding [redacted] and removing [redacted] and [redacted]	No IRB approvals of the key personnel changes were filed.
5/10/2010	AMENDMENT	AMD9	Study Personnel Change to add [redacted]	No IRB approvals of the key personnel changes were filed.
5/18/2010	AMENDMENT	AMD10	Study Personnel Change to add [redacted] and [redacted]	No IRB approvals of the key personnel changes were filed.

7/20/2010	AMENDMENT	AMD11	Study personnel change to add [redacted], [redacted], [redacted], and [redacted]	No IRB approvals of the key personnel changes were filed.
7/26/2010	CONTINUING REVIEW	CR4		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
3/1/2011	AMENDMENT	AMD 14	Waiver of Consent & HIPAA Authorization; phone script; recruitment letter (letter from Cardiologists to patients); DSMB letter	The documents submitted for Amendment 14 were found on server, but a copy of the approval letter is not on the server.
3/7/2011	AMENDMENT	AMD15	Discrepancy in the amount of blood being drawn versus the amount stated in the Consent Form and the Protocol.	Documents submitted for Amendment 15 found on server, but a copy of the approval letter is not on the server.
6/3/2011	AMENDMENT	AMD16	Study personnel change to add [redacted] and [redacted]	No IRB approvals of the key personnel changes were filed.
6/7/2011	AMENDMENT	AMD17	Study personnel change to remove [redacted]	No IRB approvals of the key personnel changes were filed.
8/5/2011	CONTINUING REVIEW	CR6	Questionnaires, Phone Script 7/28/2011, Recruitment Materials, Waiver were also approved at CR.	Could find a copy of the progress report for 2011 CR, but no other approved docs, or approval letter.
1/19/2012	AMENDMENT	AMD18	Study personnel change to remove [redacted], and [redacted].	No IRB approvals of the key personnel changes were filed.
6/14/2012	AMENDMENT	AMD19	[redacted] is leaving the REMIT study for another position at Duke and is handing over responsibility as study coordinator to [redacted].	No IRB approvals of the key personnel changes were filed.

6/22/2012	AMENDMENT	AMD20	[redacted] assumes the responsibility of a regulatory coordinator.	No IRB approvals of the key personnel changes were filed.
7/25/2012	AMENDMENT	AMD21	Study personnel change to remove [redacted]	No IRB approvals of the key personnel changes were filed.
7/26/2012	CONTINUING REVIEW	CR7		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
1/10/2013	AMENDMENT	AMD22	Study personnel change to remove [redacted]	No IRB approvals of the key personnel changes were filed.
7/3/2013	AMENDMENT	AMD23	Study personnel change to add [redacted], and [redacted]	No IRB approvals of the key personnel changes were filed.
7/11/2013	CONTINUING REVIEW	CR8		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
3/11/2014	AMENDMENT	AMD24	Proposal to conduct a metabolomic analysis of banked samples from the REMIT patients. Regression models, and pathway modeling. All analyses will be completed by study statisticians at Duke and be supervised by Dr Wei Jiang. Because we are dealing with banked samples there is no risk to the participants. This proposal was originally submitted as a new protocol, however the reviewer [redacted] suggested that submitting this as an Amendment to Pro00009555, which is still active, was more appropriate.	No approvals or documentation were filed.

3/25/2014	AMENDMENT	AMD25	Need to remove Dr. [redacted] from the REMIT Study Key Personnel	No IRB approvals of the key personnel changes were filed.
4/11/2014	AMENDMENT	AMD27	Amendment (#24) to get permission to perform metabolomic profiling on banked samples that were collected under protocol 9555. Approval received to conduct that study. However, the grant proposal that was written to support that work, so it could be examined for concordance, was not attached. NIH has notified us that we will likely receive funding for this study and have asked that we provide documentation that we have IRB approval to conduct the study as it was described in the grant as soon as possible. Attached to this Amendment are the research summary (Metabolomics Project Summary final) and the protocol that was submitted to NHLBI.	No documentation or approvals associated with this amendment could be located.
6/17/2014	AMENDMENT	AMD28	Addition of [redacted] to REMIT Study Personnel	No IRB approvals of the key personnel changes were filed.
7/17/2014	AMENDMENT	AMD29	Amendment (#27) was submitted to perform metabolic profiling on samples that were collected and banked as part of the study protocol. At that time the reviewer asked that we establish an MTA with our collaborators, [redacted], and then upload the fully executed MTA as a new amendment before transfer of samples can take place. See attachment for the MTA.	No approvals or documentation related to this amendment were filed.

9/25/2014	AMENDMENT	AMD30	Study personnel change to add [redacted] to the Key Study Personnel and remove [redacted].	No IRB approvals of the key personnel changes were filed.
1/8/2015	AMENDMENT	AMD31	study personnel change to add [redacted]	No IRB approvals of the key personnel changes were filed.
1/20/2015	AMENDMENT	AMD32	Study personnel change to remove [redacted]	No IRB approvals of the key personnel changes were filed.
3/16/2015	AMENDMENT	AMD33	Study personnel change to add [redacted] PhD to the REMIT personnel. He is statistician and will be involved in analysis of the study.	No IRB approvals of the key personnel changes were filed.
6/30/2015	AMENDMENT	AMD34	Study personnel change to add [redacted].	No IRB approvals of the key personnel changes were filed.
4/1/2016	AMENDMENT	AMD36	Study personnel change to remove [redacted]	No IRB approvals of the key personnel changes were filed.
7/12/2016	CONTINUING REVIEW	CR11		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
8/29/2016	AMENDMENT	AMD37	Study personnel change to add [redacted]	No IRB approvals of the key personnel changes were filed.
5/4/2017	AMENDMENT	AMD38	Please add [redacted] to Key Personnel.	No IRB approvals of the key personnel changes were filed.
5/31/2017	AMENDMENT	AMD39	Study personnel change to change RC/SC role from [redacted] to [redacted].	No IRB approvals of the key personnel changes were filed.
12/20/2017	AMENDMENT	AMD40	Study personnel change to remove [redacted] and [redacted] from the study.	No IRB approvals of the key personnel changes were filed.
7/14/2017	CONTINUING REVIEW	CR12		Progress reports applicable to this review, and documents approved with this review were filed, but the continuing review approval letter could not be located.
5/2/2018	AMENDMENT	AMD41	Study personnel change to remove [redacted].	No IRB approvals of the key personnel changes were filed.